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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,262	10/18/2001	C. Frank Bennett	ISPH-0612	7817

7590 06/17/2003

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F16

Office Action Summary

Application No.	Applicant(s)
09/982,262	Bennett et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 13, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5, 6*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-12 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for i.) a method of inhibiting corneal allograft rejection in a mouse or human comprising the administration of an antisense oligonucleotide between 8-50 nucleotides in length that specifically targets and inhibits the expression of ICAM-1 and for ii.) methods of preserving a corneal explant in vitro comprising incubation of explanted cornea in a composition comprising OPTISOL™ and optionally further comprising an antisense oligonucleotide between 8-50 nucleotides in length that specifically targets and inhibits the expression of ICAM-1, ELAM-1 or VCAM-1, **does not** reasonably provide enablement for methods of inhibiting corneal allograft rejections in an organism comprising the administration of an antisense oligonucleotide that specifically targets and inhibits the expression of ELAM-1 or VCAM-1, or comprising antisense oligonucleotides larger than 50 nucleobases that target ICAM-1, nor for methods of preserving a corneal explant in vitro comprising incubation of explanted cornea in a composition comprising an antisense oligonucleotide that specifically targets and

inhibits the expression of ICAM-1, ELAM-1 or VCAM-1 in the absence of OPTISOL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting corneal allograft rejections in an organism comprising the administration of an antisense oligonucleotide of any length and that specifically targets and inhibits the expression of ICAM-1, ELAM-1 or VCAM-1, and methods of preserving a corneal explant in vitro comprising incubation of explanted cornea in a composition comprising an antisense oligonucleotide of any length that specifically targets and inhibits the expression of ICAM-1, ELAM-1 or VCAM-1.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of oligonucleotide treatment applications in organisms and the state of the art regarding corneal explant storage and allografting. The high level of unpredictability regarding the prediction of oligonucleotide efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1).

Tamm et al, in a review article discussing the therapeutic potential of antisense oligonucleotides in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of oligonucleotide therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of oligonucleotides in vitro and in vivo. Furthermore, the biological effects of some chemical modifications have been studied for oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications are highly unpredictable (See Agrawal et al especially on pages 78-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

Skelnik teaches compositions comprising serum free medical solutions to maintain and preserve eye tissues, including human corneal tissues, stating that replacement of serum components in corneal preservation is a formidable challenge, and is based on over 350 known chemical components found in serum (col 1). Skelnik also teaches that the preservation of cornea is attended by epithelial decompositions and loss of corneal clarity and that a variety of storage media and techniques have been proposed, and current research continues to be directed towards maintaining and actually enhancing quality of donor tissues, but that currently there are no defined serum free media used in organ culture techniques at temperatures that allow for maintenance of corneal endothelium and barrier function of the corneal epithelium (col 1-2). In addition, Lambiase hypothesizes that the addition of Nerve Growth Factor (NGF) is essential to the maintenance of whole corneal tissue in culture, in conditions where the cornea as a whole is a morphological and functional unit comprising epithelium, stroma and endothelium, and in culture some of these cellular constituents are deprived of trophic support provided by NGF from corneal nerve endings (col 6).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of preserving a corneal explant ex vivo comprising incubating said explant in solution comprising antisense oligonucleotides target to ICAM-1, ELAM-1 and VCAM-1, in the absence of OPTISOL. Applicants have not provided guidance in the specification toward a method of inhibiting corneal allograft rejection comprising contacting the

allograft with a topical formulation comprising antisense oligonucleotides that target and inhibit the expression of ELAM-1 or VCAM-1. Applicants have not provided guidance in the specification toward a method of inhibiting corneal allograft rejection comprising contacting the allograft with a topical formulation comprising antisense oligonucleotides of lengths greater than 50 nucleobases that target and inhibit ICAM-1. The specification teaches the inhibition of corneal allograft rejection comprising contacting the allograft with a topical formulation comprising antisense oligonucleotides between 8-50 nucleobases that specifically target and inhibit the expression of ICAM-1. The specification also teaches the storage (and short term preservation) of corneal explants ex vivo comprising said explant storage in compositions comprising OPTISOL and ICAM-1 antisense oligonucleotide between 8-50 nucleobases (and at some undisclosed temperature). One skilled in the art would not accept on its face the examples given in the specification of the inhibition of corneal allograft rejection comprising contacting the allograft with a topical formulation comprising antisense oligonucleotides between 8-50 nucleobases that specifically target and inhibit the expression of ICAM-1 as being representative or correlative of the inhibition of allograft rejection comprising administration of antisense oligonucleotides that specifically target and inhibit the expression of ELAM-1 or VCAM-1, or comprising administration of antisense oligonucleotides greater than 50 nucleobases in length that target ICAM-1, in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by oligonucleotides targeting ELAM-1 or VCAM-1. One skilled in the art would not accept on its face the examples given in

the specification of methods of preserving a corneal explant ex vivo comprising incubating said explant in solution comprising OPTISOL and antisense oligonucleotides targeted to ICAM-1, ELAM-1 and VCAM-1 as being representative or correlative of the ability to preserve corneal explants in the absence of a known corneal tissue preservative solution (e.g. OPTISOL). The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with the ability to inhibit corneal allograft rejections using antisense targeting ELAM-1 or VCAM-1, or using antisense oligonucleotides greater than 50 nucleobases in length that target ICAM-1, and furthermore fails to resolve the known unpredictability in preserving corneal explants in serum free solutions and without preservative solutions well known in the art such as OPTISOL.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of inhibiting corneal allograft rejections in any organism comprising the administration of an antisense oligonucleotide of any length that specifically targets and inhibits the expression of ICAM-1, ELAM-1 or VCAM-1, and methods of preserving a corneal explant in vitro comprising incubation of explanted cornea in a composition comprising an antisense oligonucleotide of any length that specifically targets and inhibits the expression of ICAM-1, ELAM-1 or VCAM-1. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites and formulations to target appropriate cells and /or tissues, whereby inhibition of corneal allograft rejection is provided upon administration of any oligonucleotide of any length that specifically targets and

inhibits the expression of ICAM-1, ELAM-1 or VCAM. No correlation has been shown between the successful inhibition of allograft rejection using antisense to ICAM-1 and similar success using antisense to ELAM-1 or VCAM-1. Furthermore, the *de novo* determination of necessary components in serum free compositions for successfully preserving corneal explants, which preservation solutions further comprise antisense oligonucleotides (e.g. that specifically target and inhibit the expression of ICAM-1, ELAM-1 or VCAM-1), is also required. Since the specification fails to provide particular guidance for these methods, and since determination of the inhibition of corneal allograft rejections with antisense targeting VCAM-1 or ELAM-1 of any size, and with ICAM-1 antisense of lengths greater than 50 nucleobases, and preservation of corneal explants in serum free media, are highly unpredictable endeavors, it would require undue experimentation to practice the invention over the broad scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen R Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER

JZ

June 16, 2003